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APPLICATION NUMBER 20-972

MEDICAL REVIEW

NDA 20-972

Medical Officer's Review
(Original NME)

Date Submitted: June 11, 1998
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Applicant:		DuPont Pharmaceutical Company Maple Run Grove Road Wilmington, DE 19880
Drug:	Chemical:	(S)6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4- (trifluoromethyl)-2H-3,1-benzpxazin-2-one
	Generic:	Efavirenz
	Trade:	SUSTIVA ™
Route:		Oral
Dosage Form:		50 mg, 100 mg, and 200 mg capsules
Proposed Indication:		Treatment of HIV-1 infection in combination with other antiretroviral agents
Related INDs:		(b)(4)----------

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1. Resume

The applicant has requested approval for Sustiva ™, (efavirenz capsules), a non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of HIV-1 infection, when used in combination with other antiretroviral agents, under the accelerated approval regulations, 21 CFR 314 subpart H. This indication is based on surrogate endpoint analyses of plasma HIV RNA levels and CD4 cell counts in controlled studies up to 24 weeks in duration.

In support of the request for accelerated approval, the applicant has submitted the 24-week surrogate endpoint and safety data from three adequate and well controlled trials, four additional clinical trials in adults, and safety experience from an expanded access program. Data from 23 pharmacokinetic studies/ drug interaction studies were also submitted in support of the application. The applicant has submitted 12-week safety, pharmacokinetic, and efficacy data from an ongoing open-label uncontrolled trial in 57 pediatric patients ages 3 to 16 years, in support of efavirenz use in children.

The three principal controlled studies, DMP 266-006, DMP 266-020, and ACTG 364, provide adequate evidence that efavirenz in combination with other antiretroviral agents has an effect on surrogate endpoints that are reasonably likely to be associated with clinical benefit. The primary efficacy measure was the percent of patients with plasma HIV-RNA < 400 copies/ml (< 500 copies/ml in ACTG study) using the approved Amplicor ™ Monitor assay.

Study DMP 266-006 is an ongoing, open-label, randomized trial of efavirenz(EFV)/zidovudine(ZDV)/lamivudine(3TC) or efavirenz/indinavir(IDV) compared to indinavir/zidovudine/lamivudine in 450 HIV-infected patients who are naïve to efavirenz, lamivudine, other nonnucleoside reverse transcriptase inhibitors, and protease inhibitors. Seventy-one percent of patients in the EFV/ZDV/3TC arm and 63% of patients in the EFV/IDV arm compared to 55% of patients in the IDV/ZDV/3TC arm achieved HIV RNA < 400 copies/ml at 24 weeks of treatment. More patients in the IDV/ZDV/3TC arm discontinued study treatment due to adverse events compared to the other two treatment arms. It appears that part of the observed treatment effect may be due to early discontinuations in the indinavir-containing control arm. However, efavirenz containing arms certainly demonstrated efficacy comparable to the control arm. There was no significant difference in the mean CD4 cell counts among the treatment arms; the overall mean increase was 143 cells/mm^3.

Study DMP 266-020 is an ongoing, randomized, double-blind, placebo-controlled trial of 24 weeks of therapy comparing EFV/IDV/nucleoside reverse transciptase inhibitors (NRTIs) to placebo/IDV/NRTIs in 330 HIV infected patients who were NRTI-experienced, but NNRTI, and PI treatment-naïve. Physicians were allowed to add up to two NRTIs of their choice to the treatment regimen of EFV/IDV or placebo/IDV. In this study 58% of patients who received EFV/IDV/NRTIs compared to 50% of patients who received IDV/NRTIs achieved HIV RNA < 400 copies/ml at 24 weeks of treatment. Although the results were not statistically significant, they do provide supportive

evidence of efficacy. There was no significant difference in the mean CD4 cell count between treatment arms; the overall mean increase was 110 cells/mm^3.

ACTG 364 is an ongoing 48-week double-blind, placebo-controlled trial in NRTI-experienced patients who had completed two prior ACTG studies. Twenty-four week HIV RNA data for 196 patients were provided in the NDA. One treatment group received EFV in combination with nelfinavir (NFV) and two NRTIs, another received EFV and two NRTIs, and the third group received NFV and two NRTIs. Based on the proportion of patients with HIV RNA below 500 copies/ml at 24 weeks of treatment, the four drug treatment arm (EFV/NFV/2NRTIs) was superior to the three drug arm (NFV/2NRTIs). Efavirenz in combination with two NRTIs was equivalent to NFV+2NRTIs with a lower bound 95% confidence interval of –5%. The CD4 cell count change from baseline was smaller in the four drug regimen than in the other comparison groups. This seems unlikely to represent an adverse effect of efavirenz on CD4 cells. The magnitude of these CD4 cell differences was not large and these differences were not observed in other trials.

Fifty-seven patients, 3 to 16 years of age were enrolled into an ongoing 48-week trial, ACTG 382, designed to evaluate the safety, tolerability and antiviral activity of efavirenz in combination with nelfinavir. All children were NRTI-experienced and were permitted to use concomitant NRTIs. The applicant provided HIV RNA data for 48 patients at week 12 and 20 patients at week 20 of treatment. At week 12, 67% of patients had plasma HIV RNA levels < 400 copies/ml. These data are supportive of the efficacy of efavirenz in the treatment of HIV-1 infection in children when used in combination with other antiretroviral agents.

A total of 2,215 patients received efavirenz at various doses across all studies and was included in the safety database. Approximately 970 patients received efavirenz at a dose of 600 mg qd for at least 24 weeks. Phase 1 and phase 2 trials and the expanded access program supported the safety of efavirenz.

The most concerning adverse events associated with efavirenz therapy were nervous system symptoms and skin rash. Fifty-two percent of patients receiving efavirenz reported nervous system and psychiatric symptoms. These symptoms included, but were not limited to, dizziness, impaired concentration, somnolence, abnormal dreams and insomnia. These symptoms were severe in 2.6% of patients who received efavirenz 600 mg qd and in 1.4% of patients receiving control regimens. In clinical trials, 2.6% of patients discontinued therapy because of nervous system symptoms. These symptoms usually began during the first or second day of therapy and generally resolved after the first 2-4 weeks of treatment. Efavirenz should be used with caution in patients with a history of a pre-existing psychiatric disorder or drug abuse. Dosing at bedtime may improve the tolerability of these symptoms.

Skin rash was reported by 27% of adult patients treated with 600 mg qd of efavirenz compared to 17% of patients in the control groups. In clinical trials, one patient developed erythema multiforme and another patient developed Stevens-Johnson

syndrome. The incidence and severity of rash were more pronounced in the pediatric population. Rash was reported by 40% of children treated with efavirenz. Five pediatric patients discontinued treatment because of rash.

A review of the reproductive toxicity section of the NDA revealed that fetal malformations (anophthalmia, microphthalmia, and cleft palate) were observed in three of 20 fetuses/infants from efavirenz treated cynomolgus monkeys in developmental toxicity. The pregnant monkeys had plasma drug concentrations similar to those in humans dosed with 600 mg of efavirenz. Because teratogenic effects have been seen in primates at efavirenz exposures similar to those in humans at the proposed marketing dose, pregnancy should be avoided in women receiving efavirenz. There is no safety experience of efavirenz in pregnant women. Efavirenz should be used during pregnancy only in women without other therapeutic options.

The data in this application support the conclusion that efavirenz in combination with other antiretroviral agents has an effect on surrogate endpoints that are reasonably likely to be associated with a clinical benefit. Two 48-week trials evaluating long term suppression of HIV-RNA with efavirenz are underway. This new drug application was approved under the accelerated approval regulations on September 17, 1998.

2. Regulatory history

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(b)(4)---------- A discussion of the results of phase 1 and 2 trials was conducted with FDA on December 9, 1996. The sponsor met with the Division of Antiviral Drug Products Advisory Committee in closed session on July 9, 1997 to discuss adequacy of overall drug development. The sponsor returned to FDA for an End-of-Phase 2 meeting on December 1, 1997 and a Pre-NDA meeting on December 17, 1997. A rolling submission of the results of phase 1 and 2 studies was initiated in March 1998. The sponsor sought Fast Track designation on May 11, 1998 and was granted such by the FDA on May 29, 1998. On June 11, 1998, the NDA package with data through at least 16 weeks on all principal studies was submitted on paper and electronically. Subsequently, several amendments and responses have been submitted including an update containing 24-week efficacy data on all pivotal studies submitted on July 20, 1998, and a safety update submitted on August 7, 1998.

3. Summary of NDA clinical section

The clinical section of this application includes the study reports of three principal phase 3 clinical trials, four additional clinical trials in adults, one open-label study in children, an expanded access program study, and 23 pharmacokinetics/drug interaction studies.

In the three principal phase 3 studies, data are presented on 928 HIV-infected patients who entered clinical trials that compared patients on efavirenz-containing regimens with those on other antiretroviral combinations. A total of 568 patients were randomized to efavirenz-containing therapies in these studies, as depicted in the following table:

Table 1. Principal phase 3 clinical trials

Study, Location	Treatment Groups	Number of Patients	Primary Endpoint
DMP266-006, 38 sites in US, UK, Canada, & Germany	EFV 600 mg qhs + IDV 1000 mg q8h	148	Proportion of patients with < 400 copies/ml HIV-RNA at 24 weeks
	IDV 800 mg q8h + ZDV/lamivudine	148	
	EFV 600 mg qhs + ZDV/lamivudine	154	
DMP266-020, 33 sites in US, Canada, & Puerto Rico	EFV 600mg qd+IDV 1000mg q8h+NRTIs	136	Proportion of patients with < 400 copies/ml HIV-RNA at 24 weeks
	IDV 800 mg q8h + NRTIs	146	
ACTG 364, 46 sites in US	EFV 600 mg qd + 2 NRTIs	65	Proportion of patients with < 500 copies/ml HIV-RNA at 24 weeks
	NFV 750 mg tid + 2 NRTIs	66	
	EFV + NFV + 2NRTIs	65	

In addition to the three principal studies, the sponsor provided the results of the following supportive studies:

Study **DMP 266-005** was a double-blind, placebo-controlled study of 137 HIV infected adults randomized to four treatment arms and evaluated at 16 weeks of therapy by virologic and immunologic measures. Patients were randomized to EFV 600 mg, 400 mg, 200 mg or placebo in combination with zidovudine and lamivudine.

ACTG 382 is an ongoing, open-label study of efavirenz in combination with nelfinavir and NRTIs in 57 HIV-infected children ages 3 to 16 years. The purpose of the study is to determine the pharmacokinetics, safety, and efficacy of efavirenz in pediatric patients.

Study **DMP 266-004** was a double-blind, placebo controlled, dose-finding study of efavirenz 400 mg qd and 600 mg qd in combination with zidovudine and lamivudine. Ninety three HIV-infected adult patients were randomized to the three treatment arms and evaluated for safety, virology, and immunology at 16 weeks.

Study **DMP 266-024** is an ongoing, open-label study of efavirenz and nelfinavir in NRTI-naïve and NRTI experienced HIV infected adults. Sixty-two patients have been enrolled and will be followed for 48 weeks. Virologic, immunologic and safety data are presented at 16 weeks.

Study **DMP 266-003** is an ongoing, double-blind, placebo-controlled study to assess safety, tolerability, and efficacy of efavirenz 200 mg qd as monotherapy and in combination with open-label indinavir in HIV-infected adults. The study was not completed as planned due to data that supported use of efavirenz in combination therapies. Several amendments were submitted to alter treatment regimens; additional cohorts of patients were recruited.

DMP 266-903 is an ongoing, open-label expanded access program providing efavirenz for patients ages 13 and over and with advanced HIV disease. As of August 7, 1998, over 1100 patients had been enrolled and monitored for adverse events.

Phase 1 drug interaction studies of efavirenz with the following were included: saquinavir, indinavir, ritonavir, Mylanta ™, famotidine, fluconazole, clarithromycin, ethinyl estradiol, azithromycin, nelfinavir, and rifampin.

4. Phase 3 clinical trials

The review of the application included an evaluation of the analyses presented by the applicant and construction of efficacy tables from the electronic database on all patients in the principal studies. This review also included an examination of complete case report forms on patients with serious nervous system symptoms (severe depression, suicidal ideation/attempts, seizures, delusions, paranoia, and psychosis), females who became pregnant during the study, and selected patients with other nervous system adverse events and/or rash of greater than 14 days duration.

All efficacy analyses presented will describe the proportion of patients with plasma HIV-RNA (Roche Amplicor ™ assay) levels less than 400 copies/ml (for studies DMP 2(b) 006 and DMP 266-020) or 500 copies/ml (for ACTG 364) at 24 weeks of therapy. (4) (b)(4)----------
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The sponsor presented several analyses of HIV-RNA data: noncompleter equals failure, observed data, and last observation carried forward. The noncompleter equals failure method is generally viewed as the preferred analysis, because it is considered by the FDA to be the most rigorous. It will be the only method discussed in this review. The conclusions are not changed using other methods – the only difference is that response rates are higher. In the noncompleter equals failure method of analysis, all patients randomized into the study are included. Any patient whose data are missing, for any reason, is considered a failure at the time of analysis. Censoring of subjects with missing HIV-RNA data was permitted only when the subject was known to be below 400 copies/ml both before and after the missing value. All randomized subjects were included in the denominator even if they did not receive study medications.

A. Clinical trial DMP 266-006

Title: "A phase III multicenter, randomized, open-label study to compare antiretroviral activity and tolerability of three different combination regimens (DMP266 + indinavir, DMP266 + zidovudine + lamivudine, indinavir + zidovudine + lamivudine) in HIV-infected patients"

Design: This open-label, randomized study was designed to evaluate safety and efficacy of DMP266 (EFV) in combination with indinavir compared to indinavir+ZDV+3TC and secondarily EFV +ZDV+3TC to IDV+ZDV+3TC. This is an ongoing study that enrolled 1200 patients and will also be submitted in support of traditional approval. Assessment of efficacy for accelerated approval was based on the proportion of patients with HIV-RNA levels less than 400 copies/ml at 24 weeks of treatment.

HIV-infected patients with CD4 cell counts > 50 cells/ml, HIV-RNA levels >10,000 copies/ml, and with no prior exposure to EFV, 3TC, NNRTI or PI were randomized to:

Treatment 1: 600 mg EFV qhs + 1000mg IDV q8h in a fasted state
Treatment 2: 300 mg ZDV bid + 150 mg 3TC bid + 800 mg IDV q8h.
Treatment 3: 600 mg EFV qhs + 300 mg ZDV bid + 150 mg 3TC bid.

The original protocol was submitted and reviewed in October 1996, and amended as follows:

Amendment 1 - March 20, 1997: After 31 patients enrolled in Treatment 1 and drug interaction data became available, dosages were changed in that arm to 600 mg EFV qhs from 400 mg EFV qam and to 1000 mg IDV q8h from 1200 mg IDV. The sample size was increased to 120 per arm.

Amendment 2 - June 27, 1997: The sponsor extended the study for an additional 36 weeks (data not included), increased the sample size to 150 per arm, modified inclusion criteria for weight from greater than 40 kg body weight to greater than 50 kg (3TC dose recommendation change).

Endpoints: The primary endpoint was the proportion of patients achieving HIV-RNA suppression below the limit of detection (400 copies/ml on Roche Amplicor ^{TM} assay) at 24 weeks of therapy. Comparison of mean change in CD4 cell counts from baseline was the secondary endpoint.

Statistical analysis: The statistical analysis was based on the intention-to-treat principle with noncompleter=failure criteria to account for missing data. Two comparisons were analyzed: EFV + IDV with IDV + ZDV + 3TC, and EFV + ZDV + 3TC with IDV + ZDV +3TC. The study was powered to test for equivalence between the EFV + IDV and IDV + ZDV +3TC arms. For the purposes of determining sample sizes, equivalence was defined as less than 10% difference in response rates between treatment arms. Although

not specifically designed or powered to compare EFV + ZDV + 3TC with IDV + ZDV + 3TC, the design allowed such a comparison.

COMMENTS:

1. **For this study to be conducted in a blinded fashion, as originally outlined, each patient would have been required to take a total of 29 pills per day. This was considered to be impractical and to negatively affect compliance. Therefore, it was conducted as an open-label study.**
2. **This study is ongoing. Evaluation of 24 week data on 450/1200 patients is presented and is the basis for accelerated approval. The sponsor plans to present results of 48 week data for traditional approval, and extend the study for a total of 60 weeks.**

Study Population: Twelve hundred patients were randomized; the results of the first 450 are summarized in this report. Overall, 86% were male, 60% White, 19% Hispanic, 17% African-American, 68% were homosexual males, mean age of 36 years, known HIV-positive status for a mean of 3.2 years, mean baseline CD4 cell count of 345 cells/mm^3, and mean baseline HIV-RNA level of 4.77 $\log_{10}$ copies/ml (app. 58,884). There were no significant differences between study arms for gender, age, race, height, weight, years of HIV positivity, baseline CD4 cell counts or baseline HIV-RNA levels. Patients were EFV, 3TC, NNRTI, and PI-naïve at study entry. Sixty-seven patients had some prior exposure to NRTIs; 60 had prior experience with ZDV. There was no statistically significant difference in NRTI exposure rates between study arms.

COMMENT: The study arms appear well balanced at baseline with regard to demographics, HIV-RNA levels, and CD4 cell counts.

Disposition of subjects: Of 450 randomized patents, 123 (27%) discontinued therapy prematurely; 43 due to adverse events, 26 due to loss to follow-up, 21 due to protocol violation, 19 were randomized but not dosed, 12 withdrew consent, 1 for lack of effect, and 1 for reason(s) not specified. A significant increase in discontinuations attributed to adverse events was noted in the comparitor arm (IDV+ZDV+3TC); commonly due to nausea and/or other gastrointestinal complaints (18/26) or nephrolithiaisis (4/26). Overall, protocol violations were noted in 59% of subjects. The majority of violations resulted from concomitant use of prohibited medications and compliance with study medications of less than 80%. Twenty-one of the protocol violations resulted in discontinuation of therapy; no significant differences in discontinuations due to protocol violations across groups were noted.

The following two tables (2-3) depict premature discontinuations, in general, and those due to adverse events by body system. The protocol allows discontinuations for a variety of reasons, if deemed appropriate by the sponsor or investigator, including experiencing a Grade 4 AE or repeated Grade 3 AE, and, if in the investigator's opinion, it was not in the patient's best interest to continue.

Table 2. Premature Discontinuations – at 24 weeks

Reason for discontinuation (%)	EFV+IDV (N=148)	EFV+ZDV/3TC (N=154)	IDV + ZDV/3TC (N=148)
Adverse Event	7	10	26*
Protocol Violation	9	3	9
Withdrew consent	3	3	6
Failed to return	7	10	9
Lack of effect/Rx failure	1	0	0
Other	1	0	0
Randomized but not dosed	7	6	6
Total	35 (24%)	32 (21%)	56 (38%)*

Data Source: Figure 4.1, vol. 1, page 48
* Statistically significant difference from other groups, $p < 0.05$.

Table 3. Adverse events responsible for discontinuation of study drugs – by treatment group and body system – at 24 weeks

Body System (%)	EFV + IDV (N=148)	EFV +ZDV/3TC (N=154)	IDV +ZDV/3TC (N=148)
Gastrointestinal	0	3	18
Nervous system	3	3	0
Renal	0	0	4
Rash	3	1	0
Hematology/Coagulation	0	0	3
Body as Whole (fatigue, allergy)	1	2	0
Neoplasm	0	1	1
Total	7 (5%)	10 (6%)	26 (18%)

Data Source: Table 7.7, vol. 1, page 113, and review of individual patient narratives. Patient No. 38201 reclassified.

Subjects in the indinavir containing triple combination arm experienced more gastrointestinal adverse events leading to discontinuation than the other treatment arms. However, no patients who received dual therapy with indinavir and efavirenz developed gastrointestinal AEs leading to discontinuation. There was also no Grade 4 nausea, vomiting, and/or diarrhea adverse events among the three cohorts of patients.

COMMENT: It is difficult to assess the clinical significance of the AEs for which discontinuations occurred. In the control arm, 9/148 patients discontinued treatment for Grade 2 (moderate) gastrointestinal events. Nausea was the most frequent AE leading to discontinuation. Due to its subjective nature, it represents an adverse event that may be difficult to quantify. In an open-label study, some patients may have had other reasons for wishing to discontinue study therapies.

Efficacy Results

Efficacy results are based on the proportion of subjects with HIV RNA < 400 copies/ml at 24 weeks. These data can be found in the following table.

Table 4. HIV RNA results – week 24

HIV RNA levels	EFV+IDV	EFV+ZDV+3TC	IDV+ZDV+3TC
Total Randomized	148	154	148
HIV-RNA < 400 copies/ml	93 (63%)	109 (71%)	82 (55%)

COMMENT: The proportion of patients responding to EFV + ZDV + 3TC was greater than that responding to IDV + ZDV +3TC by Roche Amplicor ™ assay at 24 weeks, 71% vs. 55% (Table 4). On statistical testing comparing EFV+ZDV+3TC and IDV+ZDV+3TC, the p value was 0.006. Comparing EFV+IDV and IDV+ZDV+3TC, the results were not statistically significant. However, since there was a higher discontinuation rate in the control arm due to adverse events, the results may be somewhat confounded by the discrepancy in the discontinuation rates. Since this study was open-label, it is also possible that those dropouts were influenced by knowledge of the treatment assignment. The overall conclusions drawn from this study must be considered in light of the open-label nature of the study.

CD4 cell counts

At 24 weeks of therapy, there was no significant difference in the mean CD4 cell count among treatment groups; the mean overall increase in CD4 cell counts was 143 cells/mm^3.

Evaluation of Safety

There were no deaths during the 24-week study period. One new AIDS-defining event was noted for patient No. 14222 treated with efavirenz + ZDV + 3TC (HIV encephalopathy).

New-onset Grade 3 AEs were reported for 110 patients, 58 of whom were reported in the IDV+ZDV+3TC groups. Eight Grade 3 CNS complaints in EFV-containing arms including headaches (5), ataxia (1), convulsions (1), dizziness (1), migraine (1), and vertigo (1) were reported. Two Grade 3 rashes were reported on EFV therapy, one maculopapular, and one urticaria. For twelve patients (no difference among treatment arms) Grade 4 adverse events were reported. Granulocytopenia and hyperbilirubinemia were reported twice, otherwise no other Grade 4 events were reported more than once. No Grade 4 CNS events or rashes were reported in EFV-containing arms.

Similar percentages of patients in all groups reported new-onset AEs; 93% for EFV + IDV, 93% for EFV +ZDV + 3TC, and 93% for IDV + ZDV + 3TC as can be seen in the following table.

Table 5. New-onset Adverse Event, independent of clinician determination of causality occurring in > 10% of any group

Adverse experience	EFZ + IDV (N=148)	EFV + ZDV + 3TC (N=154)	IDV + ZDV + 3TC (N=148)
Nausea *	24 %	32 %	59 %
Fatigue *	19	29	34
Headache	22	23	26
Diarrhea	29	18	22
Dizziness *	22	27	5
Vomiting *	10	12	28
Flu-like symptoms	19	10	15
Dyspepsia	12	14	16
Maculopapular rash *	18	14	6
Insomnia *	16	14	6
Pain *	9	8	17
Sinusitis	11	10	7
Concentration impaired *	9	16	3
Depression	11	11	5
Abdominal pain	6	8	11

Data Source: Table 7.1, vol. 1, page 97.
***** Statistical differences noted between EFV-containing arm(s) and control, $p < 0.05$.

Table 6. New-onset Adverse Events by select symptom categories

Adverse experience	EFZ + IDV (N=148)	EFV + ZDV + 3TC (N=154)	IDV + ZDV + 3TC (N=148)
No. of NS AEs	167 AEs	190 AEs	105 AEs
No. pts with NS AE	71 (48%)	83 (54%)	31 (21%)
Any Rash	60 AEs	43 AEs	31 AEs
No. patients with rash	49 (33%)	44 (29%)	21 (14%)

Data Source: Table 7.1, vol. 1, page 97, Table 7.5, vol. 1, page 107, and Table 7.6, vol. 1, page 110.

Nervous system (NS) symptoms presented in Table 6 include any report of dizziness, headache, insomnia, depression, impaired concentration, nervousness, hypoaesthesia, somnolence, anxiety, euphoria, abnormal dreaming, paraesthesias, or abnormal vision. Rash includes skin disorders described as maculopapular, localized, generalized, erythematous, or dermatitis.

Adverse events responsible for discontinuations:
See Tables 2-3 above.

Adverse events due to laboratory abnormalities were reported among all three treatment arms. Hematuria, hyperbilirubinemia, and anemia were reported more frequently among patients in the control arm, and can be seen in the following table.

Table 7. Laboratory abnormalities (> 3% in any arm)

Laboratory Abnormality	EFZ + IDV (N=148)	EFV + ZDV + 3TC (N=154)	IDV + ZDV + 3TC (N=148)
Granulocytopenia	3%	6%	4%
Hematuria *	1	3	7
Hyperbilirubinemia *	1	1	8
GGT increased	4	4	1
SGOT increased	3	1	3
SGPT increased	3	1	1
Hepatic enzymes increased	1	1	3
Anemia *	0	2	4

Data Source: Table 7.1, vol. 1, page 98.
* Statistical differences noted between EFV-containing arm(s) and control.

Safety summary

Nervous system symptoms, such as dizziness, headache, insomnia, depression, impaired concentration, abnormal dreams, described as “altered sensorium” experiences, were common with approximately half of EFV-treated patients experiencing at least one such nervous system symptom on EFV compared to 21% in the comparison arm (IDV+ZDV+3TC). Nervous system experiences usually start within the first day of efavirenz therapy and resolve in the majority of patients within 3 weeks. Six patients discontinued efavirenz therapy due to nervous system AEs.

Rash was more commonly reported in each of the efavirenz-containing arms than in the IDV +ZDV + 3TC arm (31% vs. 14%). Ninety-three of 302 patients receiving efavirenz developed rash; over 90% of the rashes were Grade 1 or 2. One patient developed a Grade 4 rash on day 6 of EFV + IDV treatment. The median time to onset of rash in the efavirenz-containing arms was 10-12 days and median number of days with > Grade 1 rash was 11-16 days. Over 20% patients received medications for rash; efavirenz dose was interrupted in 20 (22%) of 93 patients with rash. Four patients discontinued efavirenz therapy due to rash.

Gastrointestinal adverse events, including nausea, vomiting, and diarrhea were reported more frequently in the IDV + ZDV + 3TC arm in addition to nephrolithiasis and hyperbilirubinemia. The discontinuation rate was significantly higher in this arm and the

difference was primarily the result of 18 discontinuations due to GI AEs, predominantly nausea, and 4 discontinuations secondary to nephrolithiasis.

Summary Conclusions of Study DMP 266-006:

The results of study DMP 266-006 support efavirenz as safe and effective therapy in combination with other antiretroviral therapies for HIV-1 infection. With a total of 450 subjects, 302 treated with efavirenz, study DMP 266-006 was a principal study powered to compare efavirenz + indinavir with indinavir + zidovudine + lamivudine. In addition, the design allowed a comparison of efavirenz + zidovudine + lamivudine to indinavir + zidovudine + lamivudine. The study arms appeared to be well balanced with respect to baseline and demographic variables. Overall, 73 % of subjects completed 24 weeks of therapy. A significant increase in discontinuations was noted in the comparison arm (IDV +ZDV +3TC) due to gastrointestinal complaints and nephrolithiasis.

Seventy-one percent of patients in EFV/ZDV/3TC arm and 63% of patients in EFV/IDV arm compared to 55% of patients in IDV/ZDV/3TC arm achieved HIV RNA < 400 copies/ml at 24 weeks of treatment. More patients in the IDV/ZDV/3TC arm discontinued study treatment due to adverse events prior to 24 weeks compared to the other two treatment arms. The results of this study suggest that efavirenz in combination with other antiretroviral agents is efficacious.

All three groups experienced significant increases in CD4 cell counts compared to baseline (overall mean increase of 143 cells/mm^3); however, no differences among treatment groups were noted.

Nervous system symptoms were noted in approximately half of patients treated with efavirenz, usually presenting on the first or second day of therapy and resolving during the first 2-3 weeks of therapy. Rash was noted in about 30% patients treated with efavirenz, generally presented during the second week of therapy and resolved during the ensuing 2-3 weeks of therapy. Elevated liver enzymes were observed in all three arms of the study, at rates less than 3 percent in each group.

B. DMP266-020

Title: "A phase 3, double-blind, placebo-controlled multicenter study to determine the effectiveness and tolerability of the combination of efavirenz and indinavir versus indinavir in HIV-infected patients receiving nucleoside analogue (NRTI) therapy"

A data set including both efficacy and safety data for 184 patients completing 24 weeks of therapy by March 4, 1998 was submitted on May 29, 1998. An efficacy update of 282 patients who completed 24 weeks of therapy and for whom HIV-RNA levels were available was submitted on July 20, 1998. A final study report with 24-week data on all 330 patients enrolled in the study will be submitted upon study completion.

Design: This ongoing, randomized, double-blind, placebo-controlled trial was conducted to compare efficacy and safety of:

Treatment 1: Efavirenz (600mg qd) + indinavir (1000mg q8h) + 1 or 2 NRTIs
Treatment 2: Indinavir (800mg q8h)+ 1 or 2 NRTIs

The study population was NRTI-experienced (at least 8 weeks), but PI and NNRTI naïve, had baseline CD4 cell counts > 50 cells/ml, and HIV-RNA levels > 10,000 copies/ml before randomization. Patients' physicians were permitted to change the NRTI regimen on day 0. Sixty seven percent of 282 patients changed NRTIs on day 0. The study was extended beyond the 24-week double-blind portion to include an additional 36-week open-label treatment period.

Endpoints: The primary endpoint was the proportion of patients achieving HIV-RNA suppression below the limit of detection (400 copies/ml on Roche Amplicor ^{TM} assay) at 24 weeks of therapy. Comparison of mean change in CD4 cell counts from baseline was the secondary endpoint.

Statistical analysis: The statistical analysis was based on the intention-to-treat principle with noncompleter=failure criteria to account for missing data.

Study population: Three hundred thirty patients were randomized; the results of the first 184 patients completing 24 weeks are summarized in this section of the report. The study groups appear well balanced with regard to demographics and HIV-related characteristics (including equal rates of change of NRTIs at day 0). The mean baseline plasma HIV-RNA level was 4.33 $\log_{10}$ copies/ml (app. 21,380) and mean baseline CD4 cell count was 325 cells/mm^3. Overall, 88% of the participants were male, and 68% were white.

No statistically significant differences between treatment arms were observed in types or duration of prior antiretroviral medications received. Overall, 90% of the subjects had prior exposure to zidovudine, 79% to lamivudine, 28% didanosine, 29% stavudine, and 27% dideoxycytidine. The mean duration of prior exposure to zidovudine was 1008 days, dideoxycytidine 834 days, didanosine 564 days, lamivudine 392 days, and stavudine 377 days. For two-thirds of patients, NRTIs were changed at baseline; the remainder continued NRTI therapies. Ninety percent of patients were treated with two NRTIs. The NRTI regimens most frequently used were 3TC + d4T (38%), ZDV+3TC (26%), and didanosine + stavudine (20%). Seven percent were treated with single NRTI therapy and four percent with triple NRTI therapy.

COMMENT: The study arms appear well balanced at baseline with regard to demographics, HIV-RNA levels, and CD4 cell counts.

Disposition of subjects: Overall, 74% of subjects completed 24 weeks of study. There were no statistically significant differences between groups regarding patients discontinuing therapy. Overall, 47 subjects discontinued therapy prematurely, 16 due to adverse events, 13 withdrew consent, nine due to protocol violations, 8 were lost to

follow-up, and one due to virologic failure. Of the 16 discontinuations due to AEs, six patients were randomized to the placebo group and ten to efavirenz arm. Of those, four patients in the EFV arm discontinued therapy due to nervous system symptoms; two in the placebo group discontinued for nervous system complaints. Three patients in the EFV arm discontinued therapy secondary to new onset of rash; one patient in the placebo group discontinued secondary to rash.

Efficacy Results

Efficacy results based on proportion of patients with HIV RNA < 400 copies/ml at week 24 can be found in the following table:

Table 8. HIV RNA results – week 24

HIV RNA levels	IDV + NRTIs	EFV + IDV + NRTIs
Total Randomized	146	136
HIV-RNA levels < 400 copies/ml	73 (50%)	79 (58%)

COMMENT: The EFV containing arm does not show a statistically significant difference from control arm based on proportion of patients with HIV-RNA levels < 400 copies/ml measured by the Roche Amplicor ™ assay. However, these results do provide supportive evidence that efavirenz has antiretroviral activity when combined with other antiretroviral agents including a protease inhibitor and NRTIs.

CD4 cell counts

The overall mean increase in CD4 cell counts from baseline was 100 cells/mm^3.

Evaluation of Safety

There were no deaths or new-onset AIDS-defining events during the study.

There were 12 serious AEs reported, five in the efavirenz containing arm and seven in the comparitor arm. Of those in the efavirenz containing arm, one was Grade 3 hepatitis, possibly drug related. The other 4 reflect disorders not likely to be drug-related, i.e., pneumonia, complications to hernia repair, and hypertension.

Ten patients in the efavirenz treated group discontinued due to adverse events. Of those, four patients in the efavirenz group discontinued therapy due to nervous system symptoms. These were generally Grade 1 or 2 events including headache, feeling "drugged", dizziness, or altered sleep patterns. One patient reported hallucinations among the CNS symptoms leading to discontinuation. Three patients had moderate rash as part of their adverse event leading to discontinuation.

The following tables (11-13) contain adverse event data reported independent of causality, by select symptom categories, and laboratory abnormality:

Table 9. New-onset Adverse Event, independent of clinician determination of causality, occurring in > 10 % of either group

Adverse Experience (%)	IDV + NRTIs (N=146)	EFV + IDV + NRTIs (N=136)
Diarrhea	24 %	34 %
Nausea	30	25
Headache	16	24
Vomiting	18	16
Pain (incl. flank)	18	16
Upper resp tract infection	19	11
Dizziness *	8	20
Maculopapular Rash	11	12
Anorexia	6	15
Pharyngitis *	16	5
Arthralgia	10	11
Reaction unclassified	11	8
Flu-like symptoms	13	5
Somnolence	8	11
Insomnia	4	13
Concentration impaired	6	12
Paraesthesia *	2	12

Data Source: Table 7.1, vol. 1, page 93.
* Statistical difference between treatment arms, $p < 0.05$.

Table 10. New-onset Adverse Events by select symptom categories

Adverse Experience	IDV + NRTIs (N=146)	EFV + IDV + NRTIs (N=136)
No. of NS AEs	63 AEs	128 AEs
No pts. with NS AE	24 (27%)	50 (54%)
Any Rash	33 AEs	27 AEs
No. pts. with rash	22 (24%)	21 (23%)

Data Source: Table 7.1, vol. 1, page 93; Table 7.5, vol. 1, page 103; and Table 7.6, vol. 1, page106.

Nervous system (NS) symptoms presented in Table 10 include any report of dizziness, headache, insomnia, concentration impaired, somnolence, paraesthesia, anxiety, depression, hypoaesthesia, dreaming abnormal, euphoria, nervousness, hallucination, or confusion. Rash includes rash, (maculopapular, localized, generalized, erythematous), bullous eruption, dermatitis, or skin disorder.

COMMENT: Nervous system symptoms appeared with a greater frequency in the efavirenz-containing arm. Rash was comparable between the study arms.

Table 11. Laboratory abnormalities (> 3% in any arm)

Laboratory abnormality (%)	IDV + NRTIs (N=146)	EFV+ IDV +NRTIS (N=136)
Creatine PK increase	6 %	4 %
Hyperbilirubinemia *	8	1
Hypertriglyceridemia	2	3
Hyperglycemia	3	2

Data Source: Table 7.1, vol. 1, page 94.
* Significant difference between treatments, $p < 0.05$

Safety summary

Nervous system AEs were quite common with approximately 54% of patients experiencing at least one nervous system symptom on EFV compared to 27% on the comparison arm. These symptoms usually started on the first or second day of therapy, continued for a mean of eight days, and included dizziness, headaches, feeling drugged, feeling "spacey" or jittery, hallucinations, insomnia, and disorientation.

Rash was reported in about one-quarter of patients in both arms and started at various times after initiation of efavirenz, the median time to onset was 27 days. The median duration was 16 days. Eefavirenz was discontinued for three patients and was interrupted in two additional patients because of rash.

Summary Conclusions of Study DMP 266-020:

Study 020 is a principal study designed to compare the safety and efficacy of efavirenz in combination with indinavir + nucleoside RT inhibitors versus indinavir + nucleoside RT inhibitors for 24 weeks. The study was well-balanced for baseline demographic, virologic and immunologic characteristics. Overall, 74 % of subjects completed 24 weeks of therapy.

Patients were NRTI experienced, and were allowed to continue on their regimen of NRTIs or change to new NRTIs at the onset of the study and at the discretion of the primary physician. No statistically significant differences between treatment arms were observed in types or duration of prior antiretroviral medications received. Patients were on a wide variety of single, double, and triple combination NRTIs in addition to efavirenz/placebo and indinavir. For two-thirds of patients, NRTIs were changed at baseline; the remaining patients continued NRTI therapies.

The results from study 020 suggest that efavirenz has antiretroviral activity when used in combination with other antiretroviral therapies for the treatment of HIV-1 infection. Three hundred thirty patients were enrolled in the study, however, only 282/330 subjects have completed 24 weeks and constitute the data reviewed. Although the EFV containing arm (EFV+IDV+NRTIs) yields a larger proportion of completers with HIV-RNA levels below 400 copies per ml (58% vs. 50% in the IDV+NRTIs arm), this difference was not statistically significant. The data are clinically relevant and provide support of the use of efavirenz in the treatment of HIV-1 infection. There was no significant difference in the mean CD4 cell count between treatment arms. The overall mean increase from baseline among the 208/282 subjects who completed 24 weeks of therapy was 110 cells/mm^3.

Nervous system symptoms were reported by one-half of patients treated with efavirenz; rash was reported by one-quarter. These adverse events generally resolved over the ensuing one to three weeks of therapy.

C. ACTG 364

Title: "Comparison of the virologic efficacy of nelfinavir and/or DMP 266 in combination with one or two new nucleoside analogs in nucleoside experienced subjects: A rollover to ACTG 302/303"

Design: Study ACTG 364 was designed as a follow-up trial for those patients in previous ACTG studies of nucleoside reverse transcriptase inhibitors (NRTIs) given as monotherapy or in two drug combinations. ACTG 364 is an ongoing, randomized, double-blind, partially placebo-controlled, multicenter study designed to evaluate the safety and efficacy of EFV + NFV +2NRTIs compared to NFV + 2NRTIs and of EFV + 2NRTIs compared to NFV +2NRTIs. Assessment of efficacy was based on the proportion of patients achieving HIV-RNA levels less than 500 copies/ml (Roche Amplicor ^{TM} assay) at 24 weeks of therapy. The total duration of study treatment will be 60 weeks. HIV-infected subjects who had participated in ACTG 302/303 and had no prior exposure to any protease inhibitor or NNRTIs were randomized to:

Treatment 1: EFV 600 mg qd + NFV placebo + 2NRTIs
Treatment 2: EFV 600 mg placebo + NFV 750 mg tid + 2 NRTIs
Treatment 3: EFV 600 mg qd + NFV 750 mg tid + 2NRTIs

NRTIs were open-label and selected to ensure that each patient received at least one new NRTI. The three possible NRTI regimens were:

Didanosine 200 mg bid + stavudine 40 mg bid
Lamivudine 150 mg bid + stavudine 40 mg bid
Didanosine 200 mg bid + lamivudine 150 mg bid

Endpoints: The primary endpoint was the proportion of patients achieving HIV-RNA suppression below 500 copies/ml on Roche Amplicor ^{TM} assay at 24 weeks of therapy.

Comparison of mean change in CD4 cell CD4 cell counts from baseline was the secondary endpoint.

The applicant submitted 16 week efficacy and safety data with the NDA. On July 20, 1998, the applicant updated information containing efficacy data on subjects for 24 weeks of therapy.

Statistical analysis: The statistical analysis was based on the intention-to-treat principle with noncompleter=failure criteria to account for missing data. EFV + NFV + 2 NRTIs was compared with NFV + 2 NRTIs. EFV + 2 NRTIs was also compared with NFV + 2NRTIs. The study was powered to test for superiority of 4 drug arm vs. NFV +2NRTIs.

Study Population: One hundred ninety-six patients were randomized. Overall, 88% were male, 74% White, 14% African-American, 9% Hispanic, mean age of 41 years, mean baseline CD4 cell count of 388 cells/mm^3, and mean baseline HIV-RNA level of 3.91 $\log_{10}$ copies/ml (app. 8,128). No significant differences between study arms for gender, race, baseline CD4 cell count or baseline HIV-RNA plasma levels were noted. Seven patients had HIV-RNA plasma levels less than 500 copies/ml at baseline (3 in the nelfinavir arm, and 2 each in the efavirenz-containing arms). Patients were NNRTI, and PI-naïve at study entry. All patients had prior exposure to NRTIs. The 196 patients enrolled and treated in ACTG 364 received the following NRTIs: Didanosine + stavudine (103 patients), lamivudine + stavudine (82), and lamivudine + didanosine (10). One patient was randomized but did not receive study medications.

COMMENT: The study arms appear well balanced at baseline with regard to demographics, HIV-RNA levels, and CD4 cell counts.

Disposition of subjects: Of the 196 randomized patients, seven (3.6%) discontinued therapy prematurely; two due to adverse events, two requested discontinuation, one due to protocol violation, one due to virologic failure, and one did not start therapy. Six of the seven patients discontinuing therapy were randomized to the four drug arm (p value < 0.05).

COMMENT: The study population represents an experienced population of subjects who have tolerated several years of treatment with NRTIs while enrolled in two consecutive ACTG studies. This study group represents a select subgroup of 196 out of 2467 patients (8%) originally entered into ACTG 175. Ninety-five percent of participants completed 24 weeks of therapy in ACTG 364. Patients in the four drug arm had a higher rate of discontinuations than the other drug arms.

Efficacy Results

Efficacy results based on proportion of patients with HIV RNA < 500 copies/ml at week 24 can be found in the following table:

Table 12. HIV RNA results – week 24

HIV RNA levels	EFV+2NRTIs	NFV + 2NRTIs	EFV+NFV+2NRTIs
Total Randomized	65	66	65
HIV-RNA < 500 copies/ml	38 (58%)	29 (44%)	46 (71%)

COMMENT: Statistical testing between EFV+NFV+2NRTIs and NFV+2NRTIs yielded a p value of 0.0015. An analysis of the proportion < 500 copies/ml between EFV + 2NRTIs and NFV + 2NRTIs was not statistically significant.

CD4 cell counts

The following table contains the results of CD4 cell counts among the treatment arms:

Table 13. CD4 cell count results – week 24

Measure	EFV+2NRTIs	NFV+2NRTIs	EFV+NFV+2NRTIs
Number studied	64	65	62
Mean change CD4 cell count from baseline	+ 80 cells/mm^3	+ 68 cells/mm^3	+ 47 cells/mm^3

COMMENT: No statistically significant differences were demonstrated in CD4 cell counts at 24 weeks among treatment groups. However, unlike the two study arms containing three drugs, the mean change in CD4 count from baseline in the EFV+NFV+2NRTIs arm was not statistically significant at 24 weeks from the baseline values. This seems unlikely to represent an adverse effect of efavirenz on CD4 cells. The magnitude of these CD4 cell differences was not large and these differences were not observed in other trials.

Evaluation of Safety

There were no deaths during the study period. Eight serious AEs were reported among patients in the EFV study arms. None of these were CNS related. One EFV patient developed erythema nodosum; another developed extensive facial swelling. Note: One of the patients in the nelfinavir arm developed Stevens Johnson Syndrome.

ACTG trials report only Grade 2 or higher AEs. There were nine patients with Grade 2, 3, or 4 AEs (14%) in the EFV arm, 12 (18%) in the NFV arm and 18 (28%) in the NFV+EFV arm.

The following table contains new onset Grade 2 or higher adverse event data reported independent of causality:

Table 14. New-Onset Grade 2 or higher Adverse Events reported independent of clinician determination of causality, by frequency of occurrence

	EFV+2NRTIs	NFV+2NRTIs	EFV+NFV+2NRTIs
Total number of patients	65	66	64
Adverse experience (%)			
Diarrhea/loose stools *	0	2 (3)	7 (11)
Ache/pain/discomfort	2 (3)	2 (3)	2 (3)
Maculopapular rash	2 (3)	1 (2)	2 (3)
Erythema/redness/inflammation	1 (2)	2 (3)	1 (2)
Dizzy/lightheaded/fainting *	4 (6)	0	0
Headache	0	1 (2)	3 (5)
Itchy/pruritus	1 (2)	2 (3)	0
Allergic rash/urticaria/hives	0	1 (2)	2 (3)

Data Source: Table 7.1, vol.1, page 58.
* Statistical significant difference among treatment groups, $p < 0.05$.

The following table lists new onset Grade 2 or higher laboratory abnormalities:

Table 15. Laboratory abnormalities - numbers of patients with a Grade 2 or higher new onset clinical laboratory measure

Laboratory Abnormality (%)	EFV + 2NRTIs (N=65)	NFV + 2NRTIs (N=66)	EFZ+NFV+2NRTIs (N=64)
CPK elevation	6 (9%)	9 (14%)	6 (9%)
Triglycerides	4 (6)	4 (6)	6 (9)
GGT elevation	1 (2)	3 (5)	3 (5)
AST elevation	2 (3)	2 (3)	1 (2)
ALT elevation	2 (3)	0 --	2 (3)
Granulocytopenia	1 (2)	2 (3)	1 (2)
Thrombocytopenia	1 (2)	0 --	2 (3)
Serum amylase	2 (3)	1 (2)	0 --

Data Source: Table 7.14, vol. 1, page 88.

COMMENT: No statistically significant differences were seen among treatment arms related to laboratory abnormalities.

Safety summary

The ACTG safety reporting system varies significantly from the applicant's reporting system used in DMP 266-006 and DMP 266-020, in that the ACTG reports only Grade 2 or higher adverse events. Using these criteria of reporting, fewer adverse events were reported in all arms of the study than those reported in the two previous studies. Nervous

system symptoms and rash were noted in both EFZ-containing arms of this study. No differences in laboratory abnormalities were reported between groups.

Summary Conclusions of ACTG 364:

ACTG 364 is an ongoing clinical trial designed to compare 48 week treatment with four drug therapy to triple therapy, i.e., EFV + NFV + 2NRTIs versus NFV + 2 NRTIs (24 week data presented here). A second analysis in this study compared EFV + 2 NRTIs with NFV + 2 NRTIs. Patients were NRTI-experienced and had completed two prior ACTG studies. The study arms were well balanced to baseline demographic, virologic, and immunologic measures. Overall, 96% of subjects completed 24 weeks of therapy. Six of the seven patients discontinuing therapy prematurely were randomized to the efavirenz/nelfinavir/2NRTI arm.

The results of study ACTG 364 support efavirenz in combination with other antiretroviral agents as safe and effective therapy in lowering viral load at 24 weeks. The four drug arm of EFV + NFV + 2 NRTIs was superior to the three drug arm of NFV + 2NRTIs at 24 weeks of therapy at the p value equals 0.0015 level. EFV + 2 NRTIs was similar to NFV + 2NRTIs at 24 weeks with regard to the proportion of patients with HIV RNA < 500 copies/ml.

There was no significant difference in the mean CD4 cell count between treatment arms; the overall mean increase was 65 cells/mm^3. Continuation of this trial to 48 weeks will help to determine whether the superiority of the four-drug regimen is maintained. These data will be reviewed as part of a traditional approval package.

Nervous system symptoms, presenting as dizziness, lightheadedness and/or fainting, were reported more commonly in the efavirenz+2NRTIs arm relative to the other two arms. No differences in rash are reported in ACTG between treatment arms.

5. Additional clinical studies

A. DMP 266-005

Title: "A phase 2, double-blind, placebo-controlled, dose-ranging study to assess the antiretroviral activity and safety of efavirenz in combination with open-label zidovudine (ZDV) and lamivudine (3TC) in HIV-infected patients"

Design: This was a placebo-controlled, randomized, double-blind, dose-ranging study conducted at 14 U.S. sites. HIV-infected patients who were asymptomatic, or mildly symptomatic, and antiretroviral-naïve, were randomized to four treatment arms:

200 mg EFV + ZDV + 3TC,
400 mg EFV + ZDV + 3TC,
600 mg EFV + ZDV + 3TC,
placebo + ZDV + 3TC.

Data through 16 weeks of therapy were reviewed. After 16 weeks of therapy, all patients were offered open-label EFV 600 mg qd.

Endpoints: The primary endpoint was the proportion of patients achieving HIV-RNA suppression below the limit of detection (400 copies/ml on Roche Amplicor ^{TM} assay) at 24 weeks of therapy. Comparison of mean change in CD4 cell counts from baseline was the secondary endpoint.

Study population: One hundred and thirty seven patients were randomized. The mean baseline CD4 cell count was 367 cells/mm^3 and mean baseline HIV-RNA level of 4.72 $\log_{10}$ copies/ml (app. 52,481). There were no significant differences between study arms for gender, age, race, height, weight, years HIV positive, HIV risk factors, baseline CD4 cell counts or baseline HIV-RNA levels. All patients were naïve to antiretroviral therapy.

Comment: The study arms appear well-balanced with regard to demographics, baseline CD4 cell counts, and HIV-RNA levels.

Disposition of subjects: Of 137 randomized patients, 23 (17%) discontinued therapy prematurely; nine due to adverse events, 7 due to loss to follow-up, 4 were non-compliant, and 3 withdrew consent. Six of the nine patients discontinuing therapy prematurely occurred in the 600 mg EFZ group. Three of the discontinuations were secondary to nervous system symptoms manifested as lightheadedness, strange dreams, dizziness, and/or "feeling stoned". One patient discontinued secondary to development of a pruritic rash.

Efficacy Results

Efficacy results based on proportion of patients with HIV RNA < 400 copies/ml at week 16 can be found in the following table:

Table 16. HIV RNA results – week 16

	Efavirenz (EFV) + ZDV + 3TC			
HIV RNA levels	EFV placebo	EFV 200 mg	EFV 400 mg	EFV 600 mg
Total Randomized	33	36	34	34
HIV-RNA < 400 copies/ml	12 (36%)	29 (81%)	25 (74%)	24 (71%)

Data Source: Table 5.2, vol.1, page 55.

COMMENT: Although the number of subjects in the study was small, the results support the antiviral effects and safety of efavirenz therapy for HIV infection.

There were no statistically significant differences noted in efficacy between 200 mg, 400 mg, and 600 mg of efavirenz.

CD4 cell counts

Mean changes in CD4 cell counts at 16 weeks were observed: +102.1 cells/mm^3 for placebo, +127.2 cells/mm^3 for EFV 200 mg, + 113.9 cells/mm^3 for EFV 400 mg, and +117.5 cells/mm^3 for EFV 600 mg.

Evaluation of Safety

There were no deaths during the 16-week, double-blind period. Two patients developed AIDS-defining events during study; one had worsening of gastric lymphoma, another developed pulmonary tuberculosis.

Eight patients receiving efavirenz developed serious AEs; most were deemed unrelated to study drug. Three patients developed serious laboratory AEs: two developed clinically significant anemia, and one granulocytopenia.

Patients in all groups reported new-onset AEs (94-100% for EFV arms vs. 97% for placebo).

The following tables (17 and 18), taken from the applicant's submission, delineate the adverse events reported in the trial:

Table 17. New onset Adverse Events, independent of clinician determination of causality, occurring in > 10% of any group

	Efavirenz (EFV) + ZDV + 3TC			
Adverse Event (%)	EFV placebo N=33	EFV 200 mg N=36	EFV 400 mg N=34	EFV 600 mg N=34
Nausea	55%	44%	47%	41%
Headache *	24	36	53	41
Fatigue	39	33	32	41
Dizziness *	18	19	29	44
Insomnia	21	25	29	15
Diarrhea	18	19	21	21
Rash *	6	22	26	24
Dyspepsia	15	11	21	26
Influenza-like symptoms	15	8	24	18
Abdominal pain	21	17	18	9
Pharyngitis	6	11	12	24
Coughing	9	14	15	15
Vomiting	15	8	15	15
Rhinitis	15	17	9	12

Table 17 (continued). New onset Adverse Events, independent of clinician determination of causality, occurring in > 10% of any group

	Efavirenz (EFV) + ZDV + 3TC			
Adverse Event (%)	EFV placebo N=33	EFV 200 mg N=36	EFV 400 mg N=34	EFV 600 mg N=34
Pain *	3%	22%	3%	18%
Anorexia	21	11	12	3
Depression	9	8	12	15
Upper resp. tract inf.	12	17	9	6
Fever	3	11	15	12
Sinusitis *	0	17	12	9
Flatulence	15	8	6	9
Myalgia	6	14	3	9
Granulocytopenia	6	8	12	6
Arthralgia	15	3	3	9
Increased sweating *	0	19	3	3
Parasthesia	3	6	15	3
Anemia	3	3	12	6
Hot flush	3	11	0	0

Data Source: Table 7.1, vol. 1, page 72. Note: All rashes were grouped.
* Statistically different from placebo, $p<0.05$

The following table lists new onset laboratory abnormalities:

Table 18. Laboratory abnormalities (> 3% in any arm)

Laboratory	Efavirenz (EFV) + ZDV + 3TC			
abnormality (%)	EFV placebo N=33	EFV 200 mg N=36	EFV 400 mg N=34	EFV 600 mg N=34
Granulocytopenia	6%	8%	12%	6%
Anemia	3	3	12	6
GGT increased	6	6	0	9
ALT increased	6	3	6	6
Hematuria	3	8	3	0

Data Source: Table 7.1, vol. 1, page 72.

Safety summary

Nervous system symptoms, rash, and elevated liver enzymes were the most notable adverse events. Nervous system symptoms included: confusion, dizziness, stupor, agitation, amnesia, depersonalizaton, euphoria, hallucinations, insomnia, somnolence,

abnormal thinking, impaired concentration, and abnormal dreams. These symptoms were variably described as feelings of dizziness, lightheadedness, or feeling "drugged." New-onset, nervous system symptoms were reported by 60 subjects (58%) in the efavirenz-containing arms and 12 subjects (36%) in the placebo arm. Subjects on higher doses of efavirenz reported more nervous system symptoms.

New-onset rash was reported in 25 patients (24%) in efavirenz-containing arms and three placebo subjects (11%).

Seven patients (including one on placebo) developed elevated liver enzymes, Grade 3 or 4 during study. Of those seven patients, two were infected with HBV and one with HCV.

Summary Conclusions of Study DMP 266-005:

Study DMP 266-005 was a phase 2 study designed to compare three doses of efavirenz and placebo in combination with ZDV and 3TC at 16 weeks. Eighty-three percent of subjects completed the 16 weeks of study treatment. Although the number of subjects in the study was small, the results support the antiviral effects and safety of efavirenz therapy for HIV infection. There were no statistically significant differences noted in efficacy between 200 mg, 400 mg, and 600 mg of efavirenz.

Treatment with efavirenz in combination with ZDV and 3TC resulted in significant decreases in HIV-RNA levels below the level of detection at 16 weeks of therapy in 76% of patients treated with the triple combination versus 36% for patients treated with ZDV and 3TC. All treatment groups experienced significant increases in CD4 cell counts compared to baseline (average increases approximately 100-120 cells/mm^3 at Week 16), however, no differences between treatment groups were noted.

In examination of the safety data, nervous system symptoms, rash, granulocytopenia and elevated liver enzymes were observed.

B. ACTG 382 (Pediatrics)

Title: "A phase I/II open-label AUC-controlled study to determine the pharmacokinetics, safety, tolerability, and antiviral activity of efavirenz in combination with nelfinavir in children"

Design: This is an ongoing 48 week, open-label, multicenter study to determine the pharmacokinetics, safety, tolerability, and antiviral activity of efavirenz capsules in combination with nelfinavir in 60 HIV-infected children less than 17 years of age. All patients were to be NRTI-experienced, NNRTI- and PI-naïve, and able to tolerate solid formulations. Subjects were permitted concomitant NRTIs. The initial targeted AUC range for efavirenz in children was between 190 and 380 uM X hours [uMxh]. This targeted lower bound was the median AUC for adults receiving EFV 600 mg QD.

Efavirenz dosage was adjusted based on tolerability and efavirenz plasma concentrations after 2 weeks of therapy. Children received an initial efavirenz dose based on body size. Nelfinavir was administered on a mg/kg basis at a dose of 20 to 30 mg/kg q8h.

Endpoints: The primary endpoint was the proportion of patients achieving HIV-RNA suppression below the limit of detection (400 copies/ml on Roche Amplicor ^{TM} assay) at 48 weeks. Comparison of mean change in CD4 cell counts from baseline was the secondary endpoint.

Study population: Fifty-seven children were enrolled in the study; 65% were female, 58% African-American, 26% Hispanic, and 16% White. The mean age at entry was 8 years (range 3-16 years). Mean baseline log $_{10}$ plasma HIV-RNA level was 4.09 (b)(4)------ $\pm$ 0.69). Mean baseline CD4 cell count was 845 cells/mm^3 (b)(4)----------

Disposition of subjects

Nine subjects discontinued therapy prematurely. Five subjects withdrew for AEs, all of which were attributed to rash/urticaria. Two patients withdrew for protocol violations, and two withdrew for virologic failure. Seven of the nine subjects withdrew within the first 2 weeks of therapy, including all five who discontinued due to AEs.

Pharmacokinetics

At 2 weeks, 25 patients had AUC values < 190 uMxh, 20 patients were between 190 and 380, and four patients were greater than 380. At 4 weeks, those with an AUC < 190 uMxh had their efavirenz dose adjusted to a target of 285 uMxh, which brought 13 of 17 subjects within the targeted AUC values.

COMMENT: The initial dose chosen was quite accurate in approaching the targeted concentration with the median AUC for children similar to that of adults.

Efficacy Results

The number and percentage of patients with HIV-RNA < 400 copies/ml were: 23/48 (67%) at week 12, and 10/20 (50%) week 20.

COMMENT: The percentage of subjects with HIV RNA < 400 copies/ml at weeks 12 and 20 was very encouraging for this patient population. As this is an ongoing clinical trial, it will be important to review the 48 week results.

CD4 cell counts

The mean change of CD4 cell counts observed from baseline for 24 patients completing 20 weeks of therapy was + 85 cells/mm^3.

Evaluation of Safety

There have been no deaths during the study. Forty-eight (84%) children reported one or more new-onset AEs.

The following table contains adverse event data reported independent of causality:

Table 19. New onset Adverse Events, independent of clinician determination of causality, occurring in > 5% of patients (N=57)

Adverse Event	Percent
Rash	42 %
Diarrhea/Loose stools	39
Fever	26
Cough	25
Nausea/Vomiting	16
Nervous system symptoms	9
Headache	9
Upper respiratory discharge	9
Abnormal breath sounds	7
Lymphadenopathy	7
“Red eye”	7

Data Source: Interim Report No. 2, Table 5.1, vol. 2, page 19.

Nervous system symptoms reported in Table 19 included dizziness, lightheadedness, fainting, lethargy, slurred speech, abnormal dreams, insomnia, and sleeping problems. No discontinuations of medications occurred secondary to these symptoms.

The folowing table lists new-onset rash by the maximum severity grade:

Table 20. Summary of new-onset Rash – by maximum severity

Maximum Severity	Number (N=57)
Grade 1 (Mild)	5
Grade 2 (Moderate)	16
Grade 3 (Severe)	2
Grade 4 (Life-threatening)	1

Source: Interim Report No. 2, Table 5.7, vol.2, page 27.

Twenty-four of 57 patients (42%) developed rash. The median time to onset of rash was 8 days (range 5-83 days). None of the patients were hospitalized for rash. The development of rash was not related to measured AUC.

Summary Conclusions of ACTG 382 (pediatrics)

This is an ongoing study in children to determine pharmacokinetics, safety, and efficacy of efavirenz in combination with nelfinavir and other antiretroviral therapies. Fifty-seven patients have been enrolled and followed for various periods of time. Although the study size is small and follow-up of short duration, the results provide pharmacokinetic results adequate to support dosing with efavirenz capsules in children ages 3 to 16 years. The pharmacokinetics of efavirenz in children aged 3-16 years is similar to those observed in HIV-infected adults.

The adverse event profile for children differs from that for adults. New onset rash, diarrhea, fever, and cough were reported in more than ten percent of children. Rash occurs at a greater frequency in children compared to adults and led to discontinuation of study medications in five children. It will be important to determine if dose reductions can lower the rates of rash in children. Nervous system symptoms were reported less commonly in children than adults, but detection of these symptoms in younger children may be limited by their ability to describe such adverse events.

C. DMP 266-004

Title: "A double-blind, placebo-controlled study to assess the safety, tolerability, and antiretroviral activity of DMP 266 in combination with open-label zidovudine and lamivudine in NRTI-experienced HIV-infected patients"

Design: This was a phase 2, placebo-controlled, double-blind study of efavirenz in combination with open-label zidovudine and lamivudine for 16 weeks in asymptomatic or mildly symptomatic HIV infected patients. The study was divided into three cohorts. In cohort 1, ten patients were randomized to 400 mg EFV qd; five patients received placebo. In cohort 2, ten patients were randomized to 600 mg EFV qd; five patients received placebo. In cohort 3, 18 patients were randomized to 600 mg EFV qd, 22 to 400 mg EFV qd, and 23 to placebo. Enrollment stopped in April 1997 as the results from other studies suggested that treatment with 2 NRTIs alone was not adequate therapy. The study was conducted at 15 sites in the USA.

Endpoints: The primary endpoint was the proportion of patients achieving HIV-RNA suppression below the limit of detection (400 copies/ml on Roche Amplicor ^{TM} assay) at week 16. All patients completing 16 weeks of therapy were offered EFV 600 mg QD open-label.

Study population: Ninety-three patients were randomized in the three cohorts. Overall, 78% of the patients were male, mean baseline CD4 cell count of 357 cells/mm^3, mean baseline HIV-RNA level was 4.01 $\log_{10}$ copies/ml (app. 10,233).

COMMENT: There was a statistically significant higher baseline HIV-RNA level for patients randomized to 400 mg EFV arm (17,378 copies/ml) relative to the other two study arms (6,918 for 600 mg EFV and 8,511 for placebo). The study arms were not balanced with regard to mean baseline HIV-RNA levels, the primary outcome measure.

Disposition of subjects: Of 93 patients randomized, 21 (23%) discontinued therapy prematurely, 4 due to adverse events (1 at 400 mg EFV, 3 at 600 mg EFV), 6 failed to return, 8 withdrew consent, two due to protocol violations, and one due to noncompliance.

Efficacy Results

Efficacy results based on proportion of patients with HIV RNA < 400 copies/ml at week 16 can be found in the following table:

Table 21. HIV RNA Results – week 16

	Efavirenz (EFV) + ZDV + 3TC		
HIV RNA levels	EFV placebo	EFV 400 mg	EFV 600 mg
Total Randomized	33	32	28
HIV-RNA < 400 copies/ml	1 (3%)	2 (6%)	9 (32%)

Evaluation of Safety

There were no deaths during the 16 week of treatment. Patients in all groups reported new-onset AEs (88% with placebo, 97% with EFV 400 mg, and 93% with EFV 600 mg).

The adverse event profile was similar to that seen in the three principal studies. Nervous system symptoms were reported for approximately half of the subjects in the efavirenz-containing arms; rash was reported for 15 percent of subjects. The most common reported adverse events were dizziness, headache, diarrhea, fatigue and insomnia.

Summary Conclusions of Study DMP 266-004:

The purpose of this study was to define a dose of efavirenz , by activity and safety, to be studied in the principal clinical trials. Based on the study results, the applicant chose to study the 600 mg dose in subsequent clinical trials.

Nervous system symptoms were reported in over half of the patients in this study treated with efavirenz; rash was reported by 15 percent of efavirenz-treated patients.

D. DMP 266-024

Title: "A phase 2, open-label, multicenter study to characterize the effectiveness, safety, and pharmacokinetics of nelfinavir in combination with DMP 266 in retroviral therapy naïve or nucleoside analogue experienced HIV-infected patients"

Design: This was a single-arm, open-label, multicenter study conducted in 32 NRTI-naïve and 30 NRTI-experienced patients to characterize decreases in plasma HIV-RNA levels, increases in CD4 cell counts, and safety of efavirenz in combination with nelfinavir. Patients received EFV 600 mg qhs and NFV 750 mg q8h for 48 weeks. Sixteen-week data were presented in the NDA.

Evaluation of Safety

No deaths were reported. Two patients developed serious AEs; one developed a Grade 3 hepatitis infection, and another had an intentional efavirenz overdose requiring hospitalization. Four patients discontinued medication prematurely; one due to Grade 3 diarrhea, one due to Grade 2 impaired concentration, one due to grade 2 fatigue and diarrhea, and one due to Grade 3 diarrhea and nausea, vomiting, and folliculitis. The most frequent new-onset AEs were diarrhea (66%), rash (35%), dizziness (18%), fatigue (13%), and flu-like symptoms (13%).

E. DMP 266-903

Title: "Efavirenz (Sustiva ^{TM}) Expanded Access Program"

This is an ongoing, open-label program to provide efavirenz HIV-infected patients with advanced disease. Patients must be 13 years of age or older, and be failing therapy or intolerant of their current antiretroviral therapy and have a CD4 cell count less than 400 cells/mm^3. All patients are to receive additional antiretroviral therapy, one other therapy to which they had never been exposed, and are not to use any other NNRTIs. No monotherapy is permitted.

Safety information on 409 patients was submitted with the NDA. The safety update submitted on August 7, 1998 contained safety data on 1,193 patients (1,150 from USA, 43 from Canada) with a cut-off date of June 1, 1998.

Demographics of patients (N=1,193) were as follows: Patients enrolled were male (93%), Caucasian (70%), African-American (16%), and Hispanic (12%). The mean nadir CD4 cell count of participants was 92 cells/mm^3, mean log $_{10}$ HIV-RNA was 4.9 (79,432 copies/ml). On average, patients entering the program had taken 7.5 antiretroviral drugs prior to study entry. Fifty percent were NNRTI-experienced prior to study entry.

The following table list the disposition of patients enrolled in the Expanded Access Program:

Table 22. Patient disposition

Number enrolled	3,448
Number receiving treatment	1,193
Total discontinuing	159 (13%)
Reasons for discontinuation	
Adverse event	103 (65%)
Death	14 (9%)
Treatment Failure	14 (9%)
Patient Request	11 (7%)
Loss to follow up	4 (3%)
Non-compliance	4 (3%)
Other	9 (6%)

Data Source: Table 4.1, vol. 7, page 14 of Safety update.

Evaluation of Safety

The purpose of this study in the NDA was to provide additional safety information in an advanced patient population with HIV disease.

Ninety-two of 1193 patients (8%) reported at least one new-onset Grade 3 or 4 adverse event. New-onset Grade 3 or Grade 4 adverse experiences by body system, and a listing of nervous system AEs are listed in the following tables:

Table 23. New-onset Grade 3 or 4 adverse experiences by body system (N=1,193)

Nervous system symptoms	20 (22%)
Rash	20 (22%)
Gastro-intestinal disorders	16 (17%)
Liver or Biliary disorders	12 (13%)
Body as a whole	12 (13%)
Other	12 (13%)

Data Source: Table 6.2, vol. 7, page 29, of Safety update.

Table 24. New-onset Grade 3 or 4 nervous system symptoms

Adverse experience (20 patients total):	
Confusion	4 (20%)
Emotional lability	4 (20%)
Hallucination	4 (20%)
Dizziness	2 (10%)
Paroniria (terrifying dreams)	2 (10%)
Psychosis	2 (10%)
Somnolence	2 (10%)

One each (abnormal gait, agitation, ataxia, convulsions, decreased libido, insomnia, and peripheral neuropathy)

Data Source: Table 6.2, vol. T, page 29, of Safety update.

Serious Grade 3 or 4 AEs were reported in 19 patients: nine from GI body site, most commonly pancreatitis; six with CNS effects, including five seizures; three cardiovascular events; and one psychiatric event – acute psychosis, suicidal ideation, and depression.

Four of the five patients with seizures as an AE were noted to have potentially confounding factors, i.e., positive cocaine drug test, PML, hypocalcemia, and history of seizure disorder.

A total of 22 patients died during the study. None of the deaths were attributed to study medications. Eleven of 22 deaths were caused by known HIV complications/AIDS-defining opportunistic infections/HIV-associated malignancies.

COMMENT: Safety data from the Expanded Access Program is reflective of the adverse event profile in the three principal clinical trials in this NDA. Nervous system symptoms and rash were the most common AEs occurring in 22% of subjects.

6. Phamacokinetic studies

Of the 23 additional studies focussing on pharmacokinetics of efavirenz, twelve were drug interaction studies. The following drugs were evaluated for the potential of a drug interaction with efavirenz: saquinavir, indinavir, ritonavir, Mylanta ™, famotidine, fluconazole, clarithromycin, ethinyl estradiol, azithromycin, nelfinavir, and rifampin.

Potentially significant drug interactions with efavirenz can occur with:

- Clarithromycin
- Ethinyl estradiol
- Indinavir
- Rifampin

- Ritonavir
- Saquinavir

Coadministration of efavirenz and clarithromycin resulted in a significant reduction in clarithromycin plasma concentrations. Plasma concentrations of ethinyl estradiol were increased when combined with efavirenz, however, the clinical significance is unknown. Indinavir plasma concentrations were decreased when indinavir was given with efavirenz. Rifampin reduced efavirenz plasma levels during co-administration. The combination of efavirenz and ritonavir was associated with a high frequency of adverse clinical and laboratory events. When saquinavir soft gelatin capsules were given with efavirenz, saquinavir levels were decreased.

COMMENT: Please see review by Dr. Sakar, the biopharmaceutical reviewer for this NDA.

Two additional pharmacokinetic studies will be reviewed. DMP 266-025 compared the pharmacokinetics and safety profile of efavirenz administered daily in the morning versus bedtime. DMP&P 98-013 evaluated CSF levels of efavirenz in HIV-positive patients.

DMP 266-025 "A phase 1 open-label study in healthy volunteers to compare the pharmacokinetics of DMP 266 administered daily in the morning versus daily administration at bedtime"

This was an open-label, randomized, two-period crossover study in which two sequential 10 day dosing periods occurred. Twenty-four men 20-42 years of age received either 400 or 600 mg efavirenz qd for 20 days, in the morning for ten days, and at bedtime for ten days.

The following table list new-onset adverse events by dosage and timing of dose.

Table 25. Treatment-related new-onset adverse events by dosage and timing

	EFV 400 mg		EFV 600 mg	
Adverse Event	AM	PM	AM	PM
Dizziness	5 (42%)	3 (25%)	4 (36%)	5 (42%)
Headache	3 (25)	2 (17)	1 (9)	0 (0)
Somnolence	2 (17)	1 (8)	2 (18)	1 (8)
Abnormal dreams	1 (8)	2 (17)	2 (18)	1 (8)
Anorexia	2 (17)	1 (8)	2 (18)	0 (0)
Hot flashes	0 (0)	1 (8)	4 (36)	0 (0)
Number of subjects				
With any AE	9/12 (75%)	7/12 (58%)	8/11 (73%)	7/12 (79%)

Data Source: Table 10.2, vol. 1, page 97.

COMMENT: No significant differences in adverse events were noted comparing dosing in the morning versus at bedtime. However, subjects treated at bedtime may better tolerate nervous system adverse events.

DM&P 98-013 "Efavirenz: Cerebrospinal fluid concentrations in HIV-positive patients"

CSF and plasma were obtained from nine patients 3.0 – 25.2 hours after an efavirenz dose at study days 28 through 295, one set of samples per patient. The CSF levels of efavirenz ranged from 6.60 – 58.94 nanomolar with plasma levels ranging from 2.21 – 8.80 micromolar. The mean CSF/plasma ratio was 0.0069 with a standard deviation of 0.0033. The CSF concentrations were directly related to the plasma concentration.

COMMENT: Efavirenz was found in the CSF and reached levels of approximately one percent of plasma levels. The clinical significance of CSF levels of efavirenz is unknown.

7. Summary of safety

There are several safety concerns when using efavirenz in combination with other antiretroviral agents in the treatment of HIV-1 infection.

Nervous system adverse events were reported by approximately 50% of patients in the principal trials treated with efavirenz in combination with other antiretroviral agents, but symptoms were generally of mild or moderate severity. These symptoms can be described as symptoms of "altered sensorium" and included dizziness, headache, insomnia, depression, concentration impairment, agitation, abnormal dreaming, and somnolence. There have also been reports of severe depression, delusions, and inappropriate behaviors, including suicide attempts, predominantly in patients with a history of mental illness or substance abuse. Dosing at bedtime improved the tolerability of these symptoms. Although there was no difference in rates of seizures between the efavirenz-treated arm and control, seizures have been reported in clinical trials, predominantly among patients with a prior history of seizures and/or patients taking other psychoactive drugs. Patients receiving treatment with efavirenz should be alerted to the potential for additive central nervous system effects if efavirenz is used concomitantly with alcohol or psychoactive drugs. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

Mild to moderate skin rashes were been reported in 27% adult patients in the principal trials treated with efavirenz compared with 17% of patients in the control group. Severe rashes with blistering, desquamation, or ulceration occurred in about 1% of patients on efavirenz. In clinical trials, one patient developed erythema multiforme and another Stevens-Johnson syndrome. Efavirenz should be discontinued for patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever.

Although not specifically studied in this NDA, appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash.

The incidence of rash and severity of rash was more pronounced in the pediatric population. Rash was reported by 42% of children treated with efavirenz. Five pediatric patients discontinued treatment because of rash.

Reproductive toxicity findings should also be highlighted. Malformations have been noted in 3 of 20 fetuses/infants from efavirenz-treated cynomolgus monkeys. The pregnant monkeys were dosed with 60 mg/kg/day throughout pregnancy, a dose comparable to recommended doses for humans. Anencephaly and unilateral anophthalmia, microopthalmia, and cleft palate were noted, respectively, in the three fetuses (**See Pharmacology Review**). There were three pregnancies reported in clinical trials, however, all pregnancies were terminated. Pregnancy should be avoided in women receiving efavirenz. If oral or other hormonal contraceptives are used, barrier contraception should always be used in combination. Efavirenz should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus and no other antiretroviral agents are available. (b)(4)----------
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In clinical trials, liver enzyme elevations greater than five times the upper limit of normal were noted at similar rates of 2-3% in efavirenz-treated and control patients. In patients treated with efavirenz 600 mg qd and seropositive for hepatitis B and/or hepatitis C virus, 13% developed ALT levels greater than five times upper limit of normal. Monitoring of liver enzymes is recommended, especially for patients with a known or suspected history of chronic hepatitis.

Because of its cytochrome P450-mediated metabolism, efavirenz should not be administered with astemizole, cisapride, ergot derivatives, midazolam, and triazolam. Other potentially significant drug interactions with efavirenz can occur with clarithromycin, ethinyl estradiol, indinavir, rifabutin, rifampin, ritonavir, saquinavir, and warfarin (**See Clinical Pharmacology/Biopharmaceutics Review**). Coadministration of efavirenz and clarithromycin resulted in a significant reduction in clarithromycin plasma concentrations. Alternatives to clarithromycin, such as azithromycin, should be considered when efavirenz is used. Plasma concentrations of ethinyl estradiol are increased when combined with efavirenz; the clinical significance of which is unknown. If ethinyl estradiol and/or other hormonal contraceptives are used with efavirenz, barrier contraception should always be used in combination (see above). When indinavir was given with efavirenz, indinavir plasma concentrations were decreased. The dose of indinavir should be increased from 800 mg to 1000 mg every eight hours when efavirenz and indinavir are co-administered. Rifampin reduced efavirenz plasma levels during co-administration in 12 healthy volunteers. The clinical significance of this interaction is unknown. Physicians should be aware of a potential clinically significant interaction when rifampin, or a related drug rifabutin, is given in combination with efavirenz. The combination of efavirenz and ritonavir was associated with a higher frequency of adverse

clinical and laboratory events. Monitoring of liver enzymes is recommended when efavirenz is used in combination with ritonavir. When saquinavir soft gelatin capsules were given with efavirenz, saquinavir levels were decreased. Use of efavirenz with saquinavir as the sole protease inhibitor is not recommended.

8. Reviewer's assessment of safety and efficacy of efavirenz

In support of the safety and efficacy of efavirenz in combination with other antiretroviral agents in adults, the applicant has submitted the results of three adequate and well controlled trials, four phase 2 clinical trials, and safety experience from an expanded access program. In support of use in pediatrics, the applicant has submitted safety and pharmacokinetic data and limited efficacy data from an open-label, uncontrolled study of efavirenz and nelfinavir in children aged 3 to 16 years.

The NDA provides clear and compelling results that demonstrate that efavirenz is effective in suppression of HIV-RNA levels in the three principal studies. The results of DMP 266-006 at 24 weeks suggest that the observed effect with triple antiretroviral treatment containing efavirenz was numerically superior to triple antiretroviral treatment containing a protease inhibitor. However, there was a higher discontinuation rate in the control arm; the imbalance appears to be related to an increase in discontinuations attributed to moderate gastrointestinal complaints. As an open-label study, it is also possible that those dropouts were influenced by knowledge of the treatment assignment. ACTG 364 is an ongoing study in NRTI-experienced patients who have completed two prior ACTG studies and represent a highly selected group of patients. In ACTG 364, a double-blind study, four drug therapy that included efavirenz and nelfinavir was superior to a three drug regimen that included nelfinavir. In addition, a three drug regimen including efavirenz was as efficacious as a three drug regimen including nelfinavir. Study DMP 266-020 did not yield a statistically significant difference in proportions of patien(b)(4)---------- ™ assay,---------- (b)(4)---------- Taken together, the three principal studies and other supportive data in the NDA package provide compelling evidence that efavirenz containing regimens are highly effective in lowering HIV RNA levels.

There will be continued discussions whether a four-drug combination of antiretrovirals has a therapeutic advantage over three drug combinations. In study ACTG 364, the efavirenz + NFV + NRTIs arm fared better than the NFV +NRTIs arm. However, in study DMP-020, efavirenz + IDV + NRTIs was not statistically superior to IDV + NRTIs in the primary analysis using Roche Amplicor ™ assay.

Although the studies were not powered to compare groups by race and gender, results favoring efavirenz-containing regimens over control regimens were maintained for three racial/ethnic groups, i.e., Caucasians, African-Americans, and Hispanics. Results favoring efavirenz-containing arms were maintained for male and female patients when data were pooled but the number of female patients entered in studies was limited in the control arms.

Efavirenz 600 mg qhs was the dosage employed for patients in the phase 3 portion of the NDA package and is the dosage recommended. In DMP 266-005, there were no statistically significant differences noted in efficacy between 200 mg, 400 mg, and 600 mg of efavirenz. In DMP 266-004, the proportion of patients achieving HIV RNA < 400 copies/ml was greater in the efavirenz 600 mg arm compared to those receiving 400 mg qd, but it must be noted that those randomized to 400 mg qd had significantly higher plasma levels of HIV-RNA at baseline.

The most concerning adverse events associated with efavirenz were nervous system symptoms and rash. Both of these adverse events were reported in all of the clinical and pharmacokinetic studies.

In the principal clinical studies, adverse events related to the nervous system were reported by 52% of patients treated with efavirenz in combination with other antiretroviral agents, but symptoms were generally mild or moderate in nature and resolved without alteration of dosing in most patients. Nervous system symptoms involved symptoms related to the central, peripheral nervous system and psychiatric symptoms. These symptoms included, but were not limited to, dizziness, headache, insomnia, depression, concentration impairment, agitation, abnormal dreaming, and somnolence. There have been reports of severe depression, delusions, and inappropriate behaviors, including suicide attempts, predominantly among patients with a history of mental illness or substance abuse. Patients receiving treatment with efavirenz should be alerted to the potential for additive central nervous system effects if efavirenz is used concomitantly with alcohol or psychoactive drugs. Patients should be instructed that if they experience nervous system symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

Mild to moderate skin rashes have been reported on patients on efavirenz. Severe rashes with blistering, desquamation, or ulceration occurred in about 1% of patients on efavirenz. Rare reports of erythema multiforme and Stevens-Johnson syndrome have been reported. The incidence of rash and severity of rash was more pronounced in the pediatric population. Rash was reported by 42% of children treated with efavirenz. Efavirenz should be discontinued for patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever.

Malformations have been noted in 3 of 20 fetuses/infants from efavirenz-treated cynomolgus monkeys. The pregnant monkeys were dosed with 60 mg/kg/day, a dose comparable to recommended doses for humans. Pregnancy should be avoided in women receiving efavirenz. Barrier contraception should always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives). Efavirenz should be used during pregnancy only if the potential benefit justifies the potential risk to (b)(4)----------
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The approval of this application is based on surrogate endpoints, i.e., analyses of plasma HIV-RNA levels and CD4 cell counts in controlled trials of up to 24 weeks in duration. Two 48-week trials evaluating long-term suppression of HIV-RNA with efavirenz are ongoing and will serve as part of the applicant's commitments for their traditional approval package, under the accelerated approval regulations.

9. Recommendations for regulatory action

This application was approved on September 17, 1998. The final label and Phase 4 commitments are provided in Appendices B and C respectively.

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Harry W. Haverkos, M.D.
Medical Officer, DAVDP

Concurrences:
HFD-530/Div Dir/HJolson
HFD-530/SMO/SKukich

CC: HFD-530/NDA 20-972
HFD-530/Div file
HFD-530/CSO/TCrescenzi
HFD-530/Pharm/KWu
HFD-530/Micro/Mishra
HFD-530/Chem/DBoring
HFD-530/Biopharm/Sekar
HFD-530/Stats/Melashoff
HFD-530/Stats/PFlyer
HFD-530/MO/TCvetkovich

Appendix A

Gastrointestinal Adverse Event grading system:

Note: Grading acute and subacute toxic effects as follows:

Nausea
- Grade 1 – Mild discomfort, maintains reasonable intake.
- Grade 2 – Moderate discomfort, significant decrease of intake, some limit of activity.
- Grade 3 – Severe discomfort, no significant food intake, activities limited
- Grade 4 – Minimal fluid intake.

Vomiting
- Grade 1 – Transient emesis.
- Grade 2 – Occasional/moderate vomiting.
- Grade 3 – Orthostatic hypotension or IV fluids required.
- Grade 4 - Hypotensive shock, hospitalization, IV fluid therapy.

Diarrhea
- Grade 1 - Transient or 3-4 loose stools/day
- Grade 2 – 5-7 loose stools/day and/or nocturnal loose stools, Rx required.
- Grade 3 – Orthostatic hypotension of > 7 stools/day or requiring IV fluids.
- Grade 4 – Hypotensive shock of hospitalization, IV fluid therapy.